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Abstract Text

Dilated cardiomyopathy is a progressive irreversible disease associated with contractile dysfunction and heart failure. During dilated cardiomyopathy, elevated diastolic wall strains trigger mechanotransduction pathways that initiate the addition of sarcomeres in series and an overall increase in myocyte length. At the whole organ level, this results in a chronic dilation of the ventricles, an increase in end diastolic and end systolic volumes, and a decrease in ejection fraction. However, how exactly changes in sarcomere number translate into changes in myocyte morphology, and how these cellular changes translate into ventricular dilation remains incompletely understood. Here we combined a chronic animal study, continuum growth modeling, and machine learning to quantify correlations between sarcomere dynamics, myocyte morphology, and ventricular dilation, see Figure 1. In an eight-week long volume overload study of six pigs, we found that the average sarcomere number increased by +3.8%/week, from 47 to 62, resulting in a myocyte lengthening of +3.3%/week, from 85 to 108um, while the sarcomere length and myocyte width remained unchanged. At the same time, the average end diastolic volume increased by +6.0%/week. Using continuum growth modeling and Bayesian inference, we correlated alterations on the subcellular, cellular, and organ scales and found that the serial sarcomere number explained 88% of myocyte lengthening, which, in turn, explained 54% of cardiac dilation. Our results demonstrate that sarcomere number and myocyte length are closely correlated and constitute the major determinants of dilated heart failure. We anticipate our study to be a starting point for more sophisticated multiscale models of heart failure. Our study suggests that altering sarcomere turnover-and with it myocyte morphology and ventricular dimensions-could be a potential therapeutic target to attenuate or reverse the progression of heart failure.

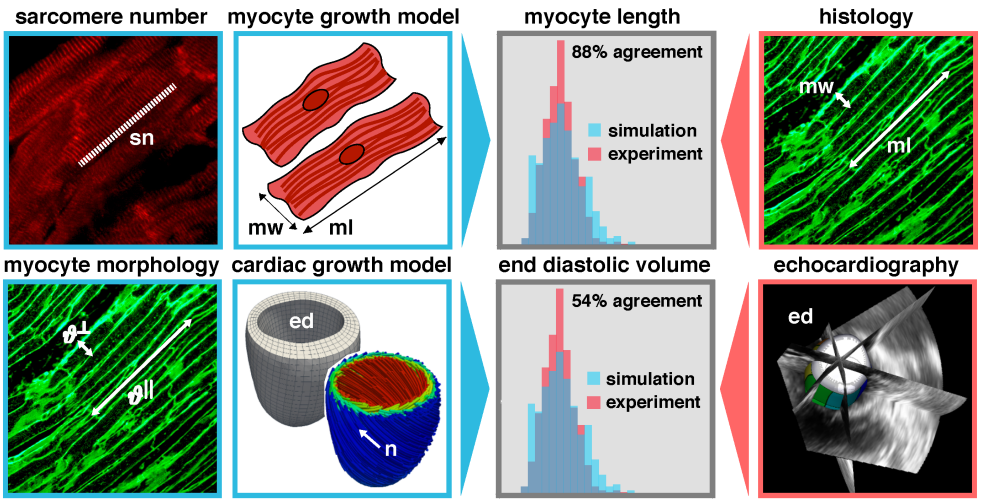

Figure 1: Bridging the subcellular, cellular, and tissue levels using a multiscale continuum growth model